



## ORIGINAL ARTICLE

# Evaluation of carotid intima-media thickness and factors associated with cardiovascular disease in children and adolescents with chronic kidney disease<sup>☆</sup>



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### KEYWORDS

Chronic kidney disease;  
Cardiovascular diseases;  
Carotid intima-media thickness;  
Adolescents;  
Children

### Abstract

**Objective:** To assess the carotid intima-media thickness and factors associated with cardiovascular disease in children and adolescents with chronic kidney disease.

**Material and methods:** Observational, cross-sectional study carried out at the Universidade Federal de São Paulo (chronic kidney disease outpatient clinics) with 55 patients (60% males) with a median age of 11.9 years (I25–I75: 9.2–14.8 years). Of the 55 patients, 43 were on conservative treatment and 12 were on dialysis. Serum laboratory parameters (creatinine, uric acid, C-reactive protein, total cholesterol and fractions, and triglycerides), nutritional status (z-score of body mass index, z-score of height/age), body fat (fat percentage and waist circumference), and blood pressure levels were evaluated. The carotid intima-media thickness measure was evaluated by a single ultrasonographer and compared with percentiles established according to gender and height. Data collection was performed between May 2015 and March 2016.

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**PALAVRAS-CHAVE**

Insuficiência renal crônica;  
Doenças cardiovasculares;  
Espessura intima-média carotídea;  
Adolescentes;  
Crianças

**Results:** Of the children and adolescents with chronic kidney disease, 74.5% (95% CI: 61.0; 85.3) showed an increase (>P95) in carotid intima-media thickness. In patients with stages I and II hypertension, 90.9% had increased carotid intima-media thickness. Nutritional status, body fat and laboratory tests were not associated with increased carotid intima-media thickness. After multivariate adjustment, only puberty (PR = 1.30,  $p=0.037$ ) and stages I and II arterial hypertension (PR = 1.42,  $p=0.011$ ) were independently associated with carotid intima-media thickness alterations.

**Conclusion:** The prevalence of increased carotid thickness was high in children and adolescents with chronic kidney disease. Puberty and arterial hypertension were independently associated with increased carotid intima-media thickness.

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### Avaliação da espessura médio-intimal da carótida e fatores associados à doença cardiovascular em crianças e adolescentes com doença renal crônica

**Resumo**

**Objetivo:** Avaliar a espessura médio-intimal da carótida e os fatores associados à doença cardiovascular em crianças e adolescentes com doença renal crônica.

**Material e métodos:** Estudo observacional transversal feito na Universidade Federal de São Paulo (ambulatórios de doença renal crônica) com 55 pacientes (60% do sexo masculino) com mediana de 11,9 anos (I25-I75: 9,2–14,8). Dos 55 pacientes, 43 estavam em tratamento conservador e 12 em terapia dialítica. Foram avaliados os parâmetros laboratoriais séricos (creatinina, ácido úrico, proteína C-reativa, colesterol total e frações e triglicérides), estado nutricional (escore z de índice de massa corpórea, escore z de estatura/idade), gordura corporal (percentual de gordura e circunferência abdominal) e pressão arterial. A medida da espessura médio-intimal da carótida foi avaliada por um único ultrassonografista e comparada com percentis estabelecidos de acordo com o sexo e a estatura. A coleta de dados foi feita entre maio de 2015 e março de 2016.

**Resultados:** Das crianças e adolescentes com doença renal crônica, 74,5% (IC 95%: 61,0; 85,3) apresentaram aumento (> P95) da espessura médio-intimal da carótida. Nos pacientes com hipertensão arterial estágios I e II, 90,9% apresentaram aumento da espessura médio-intimal da carótida. O estado nutricional, a gordura corporal e os exames laboratoriais não apresentaram associação com o aumento da espessura médio-intimal da carótida. Após ajuste multivariado, apenas a puberdade (RP = 1,30;  $p=0,037$ ) e a hipertensão arterial estágios I e II (RP = 1,42;  $p=0,011$ ) mostraram-se independentemente associados à alteração da espessura médio-intimal da carótida.

**Conclusão:** A prevalência do aumento da espessura da carótida foi elevada em crianças e adolescentes com doença renal crônica. A puberdade e a hipertensão arterial mostraram-se independentemente associadas ao aumento da espessura médio-intimal da carótida.

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**Introduction**

Cardiovascular complications are the leading cause of death in patients with chronic kidney disease (CKD). Risk factors attributed to cardiovascular disease (CVD) are important not only to identify potential alterations but also to evaluate the effect of treatments, aiming to reduce the risk of death.<sup>1</sup> The presence of traditional risk factors for CVD such as hypertension, hyperlipidemia, diabetes, physical inactivity, smoking, and advanced age is often aggravated by several nontraditional risk factors related to poor renal function such as anemia, volume overload, altered lipid metabolism (dyslipidemia), calcium-phosphorus metabolism

abnormalities (hyperparathyroidism), hyperhomocysteinemia, microalbuminuria, hyperuricemia, and chronic inflammation. All those factors increase the risk of death due to CVD in patients with CKD.<sup>2,3</sup> Children with CKD constitute a population that is less exposed to traditional cardiovascular risk factors when compared to adult patients, thus allowing a sensitive evaluation of metabolic and hemodynamic abnormalities in the pathophysiology of arteriopathic renal disease.<sup>4</sup>

Some studies have assessed the frequency of traditional risk factors for the development of CVD in children with CKD. Silverstein et al.<sup>3</sup> evaluated 45 transplanted children, all in stages 2–4 of CKD at the time of the study. They verified

that two-thirds of the patients had at least two risk factors for CVD, while one-third of them had at least three factors.

Noninvasive vascular alteration and circulatory biomarker measurement methods are important for assessing the presence and severity of cardiovascular damage and have been commonly used to study the evolution of CVD. Measurement of carotid intima-media thickness (CIMT) has become an additional tool for early detection of arterial injury and its alteration has been associated with an increased risk of coronary events and mortality in adult patients on dialysis. In pediatrics, this alteration has been reported in both patients on dialysis and in stages 2–4 of CKD.<sup>1</sup> Mitsnefes et al.<sup>5</sup> observed the carotid intima-media thickness of 31 children and adolescents after kidney transplantation and found early atherosclerosis, in addition to an association between the increase in CIMT and arterial hypertension. In a study carried out by Oh et al.<sup>6</sup> with 39 adolescents on dialysis and post-renal transplant, the carotid thickness measurement was found to be significantly higher when compared to the control group.

The increasing number of studies on the evaluation of CIMT in children and adolescents with CKD indicates this method should be introduced as a routine tool in the evaluation and monitoring of these patients. Thus, current evidence indicates that the routine assessment of cardiovascular risk is important for the early detection and treatment of vascular alterations. The present study aimed to evaluate the carotid intima-media thickness and factors associated with cardiovascular disease in children and adolescents with CKD.

## Methods

This cross-sectional, observational study included 55 patients with CKD in the dialysis and non-dialysis phases followed at the pediatric nephrology outpatient clinic of Universidade Federal de São Paulo (UNIFESP). The exclusion criteria for the study were: age <6 and ≥18 years and previous diagnosis of cardiovascular, neoplastic, infectious, or inflammatory diseases as well as systemic lupus erythematosus. Data collection was performed between May 2015 and March 2016.

The study was approved by the Research Ethics Committee of UNIFESP and the free and informed consent form as well as the term of assent were obtained from all study participants and their parents or guardians.

## Pubertal staging

Pubertal staging was evaluated by the pediatricians of the service team using as criterion the development of secondary sexual characteristics as proposed by Marshall & Tanner.<sup>7</sup>

## Blood pressure

A digital device (Dixtal<sup>®</sup>, SP, Brazil) was used for blood pressure measurement after the patient had rested for 3–5 min, with a cuff suitable for arm circumference (width and length) used at the midpoint between the olecranon and

acromion. Blood pressure was confirmed by the auscultatory method and classified according to the Clinical Practice Guideline for Screening and Control of High Blood Pressure in Children and Adolescents.<sup>8</sup>

## Nutritional status and body composition

Patients were weighed in their underwear, without shoes, on an electronic scale (Filizola<sup>®</sup>, SP, Brazil), and height was measured using a stadiometer fixed to the wall. Weight and height measures were used to calculate the z-score of body mass index (z-BMI) and z-score of height/age (z-H/A), following the reference standards and recommendations of the World Health Organization (WHO, 2007).<sup>9</sup> Body mass index (BMI) was calculated as the weight divided by squared height (kg/m<sup>2</sup>). The abdominal circumference was measured using a flexible, inextensible tape, with an accuracy of 0.1 cm and classified according to Freedman.<sup>10</sup> The body fat percentage in boys and girls was estimated using the tricipital, bicipital, subscapular, and suprailiac skinfolds, according to the Bray's equation,<sup>11</sup> and classified according to the percentile table proposed by McCarthy.<sup>12</sup> A Lange<sup>®</sup> adipometer with a precision of 1 mm (Beta Technology Inc., CA, USA) was used to measure the skinfolds.

% of Fat =  $8.71 + 0.19 \times \text{SSF}$  (subscapular skinfolds) +  $0.76 \times \text{BSF}$  (bicipital skinfolds) +  $0.18 \times \text{SupraSF}$  (suprailiac skinfolds) +  $0.33 \times \text{TSF}$  (tricipital skinfolds).

## Laboratory tests

The following laboratory parameters were analyzed in the serum after a 12-hour fast in a Cobas<sup>®</sup> C 501 equipment (Roche Diagnostics<sup>®</sup>, IN, USA): creatinine, uric acid, C-reactive protein (CRP), total cholesterol (TC), HDL cholesterol (HDL-c), and triglycerides (TG). The LDL-cholesterol fraction was obtained using the equation of Friedewald et al.<sup>13</sup>  $\text{LDL-c} = (\text{TC} - \text{HDL-c} + \text{TG}/5)$ .

The I Guideline for Atherosclerosis Prevention in Childhood and Adolescence was used to identify dyslipidemias.<sup>14</sup>

## Chronic kidney disease classification

Chronic kidney disease was classified in five stages, according to the classification proposed by the National Kidney Foundation (NKF KDOQI).<sup>15</sup>

The glomerular filtration rate was estimated by the Schwartz equation<sup>16</sup>:

$$\frac{0.413 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$$

## Ultrasonography of the carotid artery intima-media complex

Measurement of the media-intima complex thickness was performed by a single sonographer, blinded to the patient's identity and to the study group, using an ultrasound device with a linear transducer of 7 MHz of frequency and 0.1 mm resolution (General Electric<sup>®</sup>, WI, USA). The patients

remained on a stretcher in the supine position, with the head turned slightly to the contralateral side, and had a 10-min rest before the examination began. The measurement was performed on the posterior wall of the left carotid artery in the longitudinal axis, including the first echogenic line and the hypoechogenic line in the distal third of the common carotid artery, as it is a more reproducible measure, due to the fact that it does not suffer interference caused by ultrasound artifacts at the site. For the classification of carotid thickness, the table of percentiles proposed by Doyon<sup>17</sup> was used according to gender and height. Carotid intima-media thickness values >95th percentile were classified as altered.

### Statistical analysis

Initially, the prevalence of children and adolescents with CIMT alteration among those with CKD was estimated with the respective 95% confidence interval (95% CI). Qualitative variables were described as number and percentage (%), whereas the quantitative variables were described as median and interquartile range (I25; I75). Aiming to estimate the association of CIMT alterations with risk factors, the prevalence ratio (PR) and its 95% CI were calculated, with CIMT alteration as the dependent variable and the several exposure factors as the independent variables. The variables selected in the univariate analysis that showed a *p*-value <0.20 were selected to constitute the multivariate model. We chose to calculate the prevalence ratio instead of calculating the odds ratio, since the evaluated event (CIMT alteration) was frequent, i.e. with prevalence  $\geq 20\%$ . The prevalence ratios and their respective 95% confidence intervals were estimated using the generalized linear model (GLM) with binomial distribution and log link function. All tests were two-sided, and a *p*-value <5% (*p* < 0.05) was considered statistically significant. All analyses were performed using the STATA software, version 14.2 for Windows (STATA, College Station, TX, USA).

### Results

The median age was 11.9 years (I25–I75: 9.2–14.8 years). Of the 55 patients (60% males), 43 received conservative treatment and 12 were on dialysis therapy. An increase (above the 95th percentile) in CIMT was found in 74.5% (95% CI: 61.0; 85.3) of the children and adolescents with CKD. The main clinical and demographic characteristics are shown in Table 1. As shown in Fig. 1, among the patients with stage I and II arterial hypertension, 90.9% had increased CIMT. Nutritional status and body fat were not associated with increased CIMT (Table 1). Regarding laboratory tests, C-reactive protein and uric acid were elevated in 54.5% and 45.5% of patients with CKD, respectively. There was no association of increased C-reactive protein and uric acid with increased CIMT (Table 1).

Table 2 shows the variables chosen to constitute the multivariate model, that is, the ones that showed results with a *p*-value <0.2.

After the multivariate adjustment, as shown in Table 3, only puberty (PR = 1.30, 95% CI: 1.01; 0.66; *p* = 0.037) and arterial hypertension stages I and II (PR = 1.42, 95% CI: 1.08;

1.85; *p* = 0.011) were independently associated with CIMT alteration.

### Discussion

The present study with children and adolescents in stages 2–5 of CKD showed that the presence of certain risk factors for cardiovascular disease such as arterial hypertension (40%), increase in LDL cholesterol (51.9%), pubertal stage (58.2%), and inflammation (54.5%) is frequently observed. Increased thickness of the media-intima layer was evidenced in 90.9% of patients with arterial hypertension. It should be noted that arterial hypertension and puberty were the variables independently associated with increased carotid thickness in pediatric patients with CKD.

### Nutritional status and body composition

The importance of anthropometric markers is evidenced by their association with mortality and widely described in pediatric patients with CKD.

BMI is generally used as an indicator of adiposity in children and adolescents. The increase in BMI in childhood is a strong predictor of premature death due to CVD in middle and late adulthood. However, obesity-related comorbidities are more associated with the pattern of body fat distribution than with total fat mass.<sup>18</sup> Abdominal circumference is a more sensitive indicator than BMI for CVD risk assessment and is associated with atherogenicity in children and adolescents without CKD.<sup>19</sup> Although there is a higher risk of CVD in these patients, the results of this study showed no association between abdominal adiposity and body fat percentage with carotid alteration in the multivariate analysis.

In our study, 67.3% of the patients had adequate height for age. Contrary to our findings, Ku et al.<sup>20</sup> showed that children and adolescents on dialysis or after renal transplant with short stature had an increased risk of mortality, mainly due to cardiac and infectious causes.

A study carried out in the United States by Wong et al.<sup>21</sup> showed that the mortality risk increased by 14% for each unit reduction in height z-scores, regardless of the type of treatment (dialysis or transplant).

The excess fat variables (anthropometric index – BMI, and body composition – fat mass and central adiposity) and short stature were not part of the multivariate analysis. In this study, patients received dietary intervention with a nutritionist, which reflects on nutrition education and monitoring, resulting in better quality of eating among the assessed population. A recent study observed changes in nutritional status and body composition in adult patients with CKD followed for 6 months after nutritional guidance.<sup>22</sup>

### Laboratory tests

Lipid alterations have been established as a risk factor for the development of atherosclerosis. The association between dyslipidemia and increased carotid intima-media thickness has been evidenced in studies with children. Brady et al. evaluated pediatric patients in stages 2–4 of CKD and demonstrated this association.<sup>23</sup> In the study by

**Table 1** Demographic, clinical, anthropometric, and laboratory characteristics of pediatric patients with chronic kidney disease, according to the presence of carotid intimal-media thickness alteration.

	Altered carotid/height (n = 41)					
	Total	N	%	PR	95% CI	p
<b>Demographic characteristics</b>						
<i>Gender</i>						0.803
Female	22	16	72.7	1.00		
Male	33	25	75.8	1.04	0.76–1.43	
<i>Age (years)</i>						0.615
Median (I25; I75)	11.9 (9.2; 14.8)	11.1 (9.2; 14.7)	0.99	0.94–1.03		
<i>Age range</i>						0.400
<12 years	29	23	79.3	1.00		
≥12 years	26	18	69.2	0.87	0.64–1.20	
<i>Pubertal stage</i>						0.063
Prepubertal	32	21	65.6	1.00		
Pubertal	23	20	87.0	1.32	0.98–1.78	
<b>Clinical characteristics</b>						
<i>Etiology of CKD</i>						
Urinary tract malformation	30	25	83.3	1.00		
Glomerulopathy	7	6	85.7	1.03	0.73–1.45	0.872
Others	18	10	55.6	0.67	0.43–1.04	0.073
<i>Time of CKD (years)</i>						0.520
Median (I25; I75)	5.5 (2.1; 9.0)	5.0 (2.0; 9.0)	0.99	0.95–1.03		
<i>Duration of CKD</i>						>0.999
<1 year	5	4	80.0	1.00		
1–2 years	6	5	83.3	1.04	0.59–1.83	0.888
2–5 years	15	11	73.3	0.92	0.54–1.56	0.749
≥5 years	29	21	72.4	0.90	0.55–1.48	0.692
<i>Treatment</i>						0.738
Conservative	43	32	74.4	1.00		
Peritoneal dialysis	5	3	60.0	0.81	0.38–1.68	
Hemodialysis	7	6	85.7	1.15	0.81–1.63	
<i>CKD stage</i>						0.341
Stage 2	10	5	50.0	1.00		
Stage 3A	7	5	71.4	1.43	0.66–3.11	
Stage 3B	12	9	75.0	1.50	0.74–3.02	
Stage 4	10	9	90.0	1.80	0.94–3.46	
Stage 5	16	13	81.2	1.62	0.84–3.15	
<b>Clinical characteristics</b>						
<i>Blood pressure classification<sup>a</sup></i>						0.124
Normal	28	18	64.3	1.00		
Elevated	5	3	60.0	0.93	0.43; 2.01	0.860
Stage I arterial hypertension	17	15	88.2	1.37	0.99; 1.90	0.057
Stage II arterial hypertension	5	5	100.0	–		
<i>Blood pressure classification<sup>a</sup></i>						0.016
Normal or elevated	33	21	63.6	1.00		
Stage I or II hypertension	22	20	90.9	1.43	1.07; 1.91	
<b>Anthropometric indexes</b>						
<i>BMI<sup>b</sup> / Age z</i>						
Median (I25; I75)	–0.6 (–1.5; +0.5)	–1.0 (–1.5; –0.1)				
<i>Nutritional status<sup>c</sup></i>						0.003
Thinness	7	5	71.4	0.82	0.51; 1.34	0.440
Normal weight	37	32	86.5	1.00		
Excess weight	11	4	36.4	0.42	0.93; 1.19	0.032

Table 1 (Continued)

	Altered carotid/height (n = 41)					
	Total	N	%	PR	95% CI	p
<i>Height/age z</i>						
Median (I25; I75)	-1.0 (-2.6; -0.0)	-1.2 (-2.6; -0.2)	0.96	0.89-1.03		0.290
Adequate	35	26	74.3	1.00		
Short stature (<-2)	20	15	75.0	1.01	0.73-1.39	
<i>Adiposity</i>						
<i>Abdominal circumference (cm)<sup>d</sup></i>						
Median (I25; I75)	60.2 (56.0; 69.2)	59.0 (56.0; 67.0)	-			
Adequate (<P90)	53	41	77.4	-		
Elevated (≥P90)	2	0	0.0	-		
<i>Body fat (%)</i>						
Median (I25; I75)	18.9 (17.4; 24.1)	18.3 (17.3; 20.2)	0.97	0.94-1.00		0.044
<i>Body fat<sup>e</sup></i>						
Low deposit of fat	1	1	100.0	-		
Adequate	42	35	83.3	1.00		
Excess	4	2	50.0	0.60	0.22; 1.61	0.312
Obesity	8	3	37.5	0.45	0.18; 1.11	0.084
<i>Laboratory tests</i>						
<i>Uric acid (mg/dL)</i>						
Median (I25; I75)	5.5 (5.0; 6.6)	5.2 (4.9; 6.3)	0.91	0.80; 1.04		0.178
<i>Uric acid</i>						
≤5.7	30	25	83.3	1.00		0.122
>5.7	25	16	64.0	0.77	0.55; 1.07	
<i>CRP (mg/L)</i>						
Median (I25; I75)	1.1 (0.6; 2.2)	1.0 (0.6; 2.7)	1.01	1.00; 1.01		<0.001
<i>CRP</i>						
≤1	25	20	80.0	1.00		0.392
>1	30	21	70.0	0.87	0.64; 1.19	
<i>Total cholesterol (mg/dL)</i>						
Median (I25; I75)	175.0 (150.0; 201.0)	177.0 (151.0; 208.0)	-			
<i>Total cholesterol<sup>f</sup></i>						
Desirable	12	9	75.0	1.00		0.442
Borderline	13	8	61.5	0.82	0.48; 1.41	0.473
Increased	30	24	80.0	1.07	0.73; 1.55	0.734
<i>LDL (mg/dL)<sup>f</sup></i>						
Median (I25; I75)	102.0 (85.0; 126.0)	108.5 (86.5; 131.5)	-			
<i>LDL (mg/dL)<sup>a</sup></i>						
Desirable	26	18	69.2	1.00		0.394
Borderline	17	12	70.6	1.02	0.68; 1.52	0.924
Increased	11	10	90.9	1.31	0.96; 1.80	0.092
<i>HDL (mg/dL)</i>						
Median (I25; I75)	47.0 (39.0; 54.0)	47.0 (39.0; 54.0)	1.00	0.98; 1.01		0.698
<i>HDL (mg/dL)<sup>f</sup></i>						
≥45 mg/dL	34	25	73.5	1.00		0.826
<45 mg/dL	21	16	76.2	1.04	0.76; 1.42	
<i>Triglycerides (mg/dL)</i>						
Median (I25; I75)	108.0 (73.0; 142.0)	108.0 (76.0; 138.0)	-			
<i>Triglycerides<sup>f</sup></i>						
Desirable	23	17	73.9	1.00		0.234
Borderline	13	12	92.3	1.25	0.93; 1.67	0.132
Increased	19	12	63.2	0.85	0.56; 1.30	0.464

Interquartile (I25-I75); PR, prevalence ratio; 95% CI, 95% confidence interval.

<sup>a</sup> Flynn et al., 2017.<sup>8</sup>

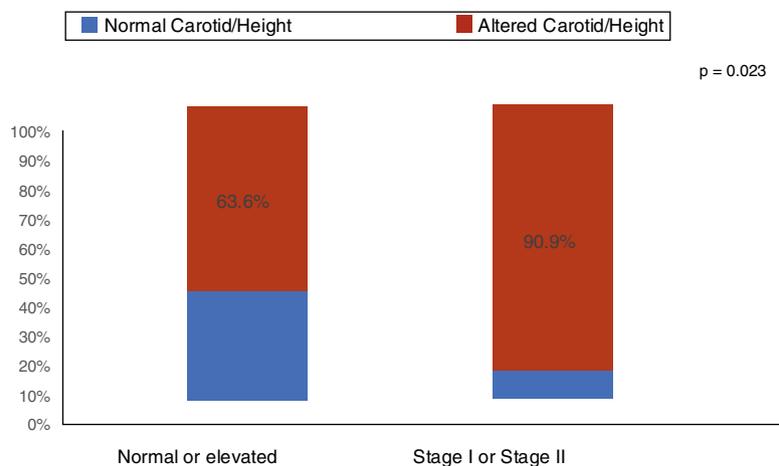
<sup>b</sup> Body mass index (BMI).

<sup>c</sup> WHO, 2006.<sup>9</sup>

<sup>d</sup> Freedman et al., 1999.<sup>10</sup>

<sup>e</sup> McCarthy et al., 2006.<sup>12</sup>

<sup>f</sup> Giuliano et al., 2005.<sup>14</sup>



**Figure 1** Blood pressure and carotid intima-media thickness alteration in pediatric patients with chronic kidney disease.

**Table 2** Univariate analysis of factors associated with increased carotid intima-media thickness in pediatric patients with chronic kidney disease.

	Univariate	
	bPR (95% CI)	<i>p</i>
Pubertal stage – Pubertal × Prepubertal	1.32 (0.98; 1.78)	0.063
<i>CKD etiology</i>		
Glomerulopathy × Malformation	1.03 (0.73; 1.45)	0.872
Others × Malformation	0.67 (0.43; 1.04)	0.073
<i>CKD stage</i>		
Stage 3A or 3B × Stage 2	1.47 (0.75; 2.89)	0.261
Stage 4 × Stage 2	1.80 (0.94; 3.46)	0.078
Stage 5 × Stage 2	1.62 (0.84; 3.15)	0.151
%Body Fat	0.97 (0.94; 1.00)	0.044
Blood pressure Stage I or II Hypertension × Normal or Elevated	1.43 (1.07; 1.91)	0.016
CRP	1.01 (1.00; 1.01)	<0.001
<i>LDL</i>		
Borderline × Desirable	1.02 (0.68; 1.52)	0.924
Increased × Desirable	1.31 (0.96; 1.80)	0.092

bPR, crude prevalence ratio (univariate model).

**Table 3** Multivariate analysis of factors associated with increased mean carotid intima-media thickness in pediatric patients with chronic kidney disease.

	Multivariate	
	adjPR (95% CI)	<i>p</i>
Pubertal stage – Pubertal × Prepubertal	1.30 (1.01; 0.66)	0.037
Blood pressure Stage I or II Hypertension × Normal or Elevated	1.42 (1.08; 1.85)	0.011

adjPR, adjusted prevalence ratio (multivariate model).

Khandelwal et al.,<sup>24</sup> the association of increased carotid media-intima thickness, triglycerides, total cholesterol, and LDL cholesterol was found in children at different stages of CKD.

In this study, LDL cholesterol showed an association with altered carotid thickness in the univariate analysis, but the multivariate analysis did not confirm this association.

Inflammation is one of the events responsible for CVD in CKD, and high levels of inflammatory markers are identified in children undergoing dialysis.<sup>25</sup> Our findings demonstrated that although high levels of CRP showed an association with altered carotid thickness in the univariate analysis, no association was observed in the multivariate analysis.

Hyperuricemia has been widely studied in patients with CKD, as it is a modifiable cardiovascular risk factor and plays a significant role in endothelial dysfunction, inflammation and atherosclerosis.<sup>18</sup> In our study, 45.5% of the patients had hyperuricemia, and this marker was not associated with altered carotid thickness.

### Arterial hypertension and puberty

Systemic arterial hypertension (SAH) is one of the most critical determinants of renal disease progression in children and a major risk factor for cardiovascular complications. The literature findings show a correlation between high blood pressure and signs of arterio/atherosclerosis in children, being one of the most important modifiable factors among the risk factors for CVD.<sup>26</sup>

Our study showed that of the 40% of stages I and II hypertensive patients 90.4% had an increase in carotid thickness, whereas in the group with normal or elevated blood pressure more than 50% (63.6%) of patients already had an increase in the carotid intima-media thickness. When comparing the two groups, a statistically significant difference was observed in the proportions of the media-intima layer alteration ( $p=0.023$ ). Arterial hypertension is a frequent finding in patients with CKD and several studies have demonstrated this risk factor for cardiovascular complications. In the study by Flynn et al.<sup>27</sup> including 586 children with CKD, it was observed that arterial hypertension was present in 54% of the patients. Despite the use of antihypertensive medication, 48% of these children showed inadequate blood pressure control. Another North American study with pediatric transplant patients showed that 48% of uncontrolled arterial hypertension at CKD onset increased to 50–75% in the final stage of CKD. After transplantation, the reported prevalence of hypertension was 50–87%.<sup>28</sup>

Carotid artery alterations were also confirmed by Brady et al.,<sup>23</sup> who assessed risk factors for CVD and found that arterial hypertension was significantly associated with increased carotid thickness in children aged 2–18 years with CKD. Poyrazoglu et al.<sup>29</sup> assessed the carotid media-intima thickness of 34 children with CKD and found an increase in CIMT in this population, as well as an association between increased CIMT and arterial hypertension.

As for pubertal staging, pubertal patients (G2/M2–G5/M5) showed a greater association with increased carotid thickness (PR = 1.30; 95% CI: 1.01; 0.66;  $p=0.037$ ). In a study with healthy children carried out by Baroncini et al.<sup>30</sup> it was observed that carotid thickness alterations were associated with increased age, as seen in adults. These findings could be related to the fact that at puberty, hormonal changes may induce an increase in the percentage of total body fat and alterations in lipoproteins, especially LDL-c increase.<sup>30</sup> Another possible explanation would be that CIMT increases in response to the physiological vessel reaction in order to adapt to the blood pressure increase that occurs with advancing age.<sup>17</sup> Moreover, in a study with 24 children with CKD carried out by Bilginer et al.,<sup>28</sup> an association was found between the time of CKD and the increase in CIMT.

Among the limitations of this study, a larger sample size could provide greater power and lower confidence intervals. Another limitation is the fact that, if the study had a control group, the occurrence of CVD risk factors non-specific to CKD could be compared in the group of studied patients.

We conclude that puberty and arterial hypertension are important determinants in CIMT increase. Moreover, the assessed risk factors play an important role in CVD-associated morbidity and mortality in children with CKD. The implications of these findings require investigation in further studies. However, early and routine assessment of these factors, together with appropriate intervention, is crucial to prevent CVD progression and mortality in these patients.

### Conflicts of interest

The authors declare no conflicts of interest.

### References

- Shroff R, Dégi A, Kerti A, Kis E, Cseprekál O, Tory K, et al. Cardiovascular risk assessment in children with chronic kidney disease. *Pediatr Nephrol.* 2013;28:875–84.
- Dégi A, Kerti A, Kis E, Cseprekál O, Tory K, Szabó AJ, et al. Cardiovascular risk assessment in children following kidney transplantation. *Pediatr Transplant.* 2012;16:564–76.
- Silverstein DM, Mitchell M, LeBlanc P, Boudreaux JP. Assessment of risk factors for cardiovascular disease in pediatric renal transplant patients. *Pediatr Transplant.* 2007;11:721–9.
- Litwin M, Wühl E, Jourdan C, Niemirska A, Schenk JP, Jobs K, et al. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. *Nephrol Dial Transplant.* 2008;23:2552–7.
- Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Abnormal carotid artery structure and function in children and adolescents with successful renal transplantation. *Circulation.* 2004;110:97–101.
- Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation.* 2002;106:100–5.
- Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls and boys. *Arch Dis Child.* 1969;44:291–303.
- Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140:e20171904.
- World Health Organization. WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Methods and development. Geneva, Switzerland: WHO; 2006.
- Freedman DS, Serdula MK, Srinivasan SR, Berenson GS. Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. *Am J Clin Nutr.* 1999;69:308–17.
- Bray GA, DeLany JP, Harsha DW, Volaufova J, Champagne CC. Evaluation of body fat in fatter and leaner 10-y-old African American and white children: the Baton Rouge Children's Study. *Am J Clin Nutr.* 2001;73:687–702.
- McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. *Int J Obes.* 2006;30:598–602.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma,

- without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
14. Giuliano IC, Caramelli B, Pellanda L, Duncan B, Mattos S, Fonseca FH. I Diretriz de prevenção da aterosclerose na infância e adolescência. *Arq Bras Cardiol*. 2005;85:S4–36.
  15. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis*. 2002;39:S1–266.
  16. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *JASN*. 2009;20:629–37.
  17. Doyon A, Kracht D, Bayazit AK, Deveci M, Duzova A, Krmar RT, et al. 4C Study consortium. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. *Hypertension*. 2013;62:550–6.
  18. Navaneethan SD, Beddhu S. Associations of serum uric acid with cardiovascular events and mortality in moderate chronic kidney disease. *Nephrol Dial Transplant*. 2009;24:1260–6.
  19. Maffei C, Banzato C, Talamini G. Waist-to-height ratio, a useful index to identify high metabolic risk in overweight children. *J Pediatr*. 2008;152:207–13.
  20. Ku E, Fine RN, Hsu CY, McCulloch C, Glidden DV, Grimes B, et al. Height at first RRT and mortality in children. *Clin J Am Soc Nephrol*. 2016;11:832–9.
  21. Wong CS, Gipson DS, Gillen DL, Emerson S, Koepsell T, Sherard DJ, et al. Anthropometric measures and risk of death in children with end-stage renal disease. *Am J Kidney Dis*. 2000;36:811–9.
  22. Pérez TA, González GE, García LH, Del Peso G, López-Sobaler AM, Selgas R. Improvement in nutritional status in patients with chronic kidney disease-4 by a nutrition education program with no impact on renal function and determined by male sex. *J Ren Nutr*. 2017;27:303–10.
  23. Brady TM, Schneider MF, Flynn JT, Cox C, Samuels J, Saland J, et al. Carotid intima-media thickness in children with CKD: results from the CKiD study. *Clin J Am Soc Nephrol*. 2012;7:1930–7.
  24. Khandelwal P, Murugan V, Hari S, Lakshmy R, Sinha A, Hari P, et al. Dyslipidemia, carotid intima-media thickness and endothelial dysfunction in children with chronic kidney disease. *Pediatr Nephrol*. 2016;31:1313–20.
  25. Goldstein SL, Currier H, Watters L, Hempe JM, Sheth RD, Silverstein D. Acute and chronic inflammation in pediatric patients receiving hemodialysis. *J Pediatr*. 2003;143:653–7.
  26. Litwin M, Niemirska A. Intima-media thickness measurements in children with cardiovascular risk factors. *Pediatr Nephrol*. 2009;24:707–19.
  27. Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, et al., Chronic kidney disease in children study group. Blood pressure in children with chronic kidney disease: a report from the chronic kidney disease in children study. *Hypertension*. 2008;52:631–7.
  28. Bilginer Y, Ozaltin F, Basaran C, Aki TF, Karabulut E, Duzova A, et al. Carotid intima-media thickness in children and young adults with renal transplant: internal carotid artery vs. common carotid artery. *Pediatr Transplant*. 2007;11:888–94.
  29. Poyrazoğlu HM, Düşünsel R, Yikilmaz A, Narin N, Anarat R, Gündüz Z, et al. Carotid artery thickness in children and young adults with end stage renal disease. *Pediatr Nephrol*. 2007;22:109–16.
  30. Baroncini LA, Sylvestre LC, Pecoits FR. Assessment of intima-media thickness in healthy children aged 1 to 15 years. *Arq Bras Cardiol*. 2016;106:327–32.